

EDITORIAL COMMENT

Autonomic Modulation Preceding the Onset of Atrial Fibrillation*

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Autonomic influences on the heart have been recognized for many centuries. It was not until 1921, however, that a German physiologist named Otto Loewi stimulated a frog's vagus nerve, collected the released substance, and applied it to a second, different frog heart to demonstrate its effects. For his discovery of this "vagusstuff" (subsequently shown to be acetylcholine), Loewi (1) shared the 1936 Nobel Prize in Physiology or Medicine. We now know that acetylcholine released by the vagus nerve is the predominant parasympathetic influence on the heart while epinephrine and norepinephrine mediate the principal cardiac sympathetic effects (2).

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The measurement of autonomic tone in humans noninvasively presented new challenges. Subtle beat-to-beat variations in heart rate are influenced by autonomic tone, giving rise to the measure of heart rate variability (HRV). That changes in the RR-interval (heart rate) precede and predict clinically relevant events was first appreciated in the mid-1960s when beat-to-beat variations in heart rate were shown to portend fetal distress (2). Later, it was appreciated that reduced HRV was an independent predictor of ventricular arrhythmias, sudden cardiac death, and total mortality after myocardial infarction and predicted increased mortality in other patient populations such as those with heart failure or diabetes (2–4).

Experimental studies utilizing vagus nerve stimulation, vagotomy, and muscarinic receptor blockade have demonstrated that efferent vagal activity contributes significantly to the high-frequency (HF) component of HRV (2). While interpretation of the low-frequency (LF) component of HRV is more controversial, most agree that at least some portion reflects sympathetic modulation of the autonomic nervous system (2). The LF/HF ratio is viewed by many, therefore, to represent sympathovagal "balance" (2). Importantly, HRV measures changes in the relative degree of autonomic modulation of heart rate, not the absolute level of sympathetic or parasympathetic tone.

In this issue of the *Journal*, Amar et al. (5) report the results of their investigation into the autonomic fluctuations preceding the development of postoperative atrial fibrilla-

tion (AF) in patients undergoing major thoracic surgery. They utilized HRV measures as an indicator of autonomic tone. Compared with control patients, those who developed AF had an increase in LF and HF power and a decrease in LF/HF ratio in the period preceding AF onset. These findings are consistent with activation of both the sympathetic and parasympathetic systems with a shift towards parasympathetic predominance. These findings add to the growing body of literature suggesting that autonomic influences play an important role in the initiation of AF.

A number of other studies have also demonstrated that fluctuations in autonomic tone, as measured by HRV, precede the onset of AF (6–10). Yet while these investigations consistently demonstrate that dynamic changes in autonomic tone occur prior to AF, the frequency, character, and degree of change varies considerably from study to study. For example, among patients with structurally normal hearts, some have observed an increase in vagal predominance in the minutes preceding AF onset, while others have noted a marked shift towards sympathetic predominance (10,11). Other patients with paroxysmal AF or AF triggered by pulmonary vein foci may experience a rise in sympathetic tone followed by a marked shift towards vagal predominance in the minutes preceding AF onset (6,7), findings more consistent with those of Amar et al. In contrast, patients undergoing cardiac surgery experience a relative decrease in vagal tone and an increase in sympathetic tone before developing AF (9). To explain these various observations, some have suggested that vagally mediated AF occurs most often in patients with normal hearts and occurs predominantly at night when vagal tone is relatively high, while adrenergically induced AF occurs more frequently in patients with organic heart disease and occurs more frequently during the day (11). However, not all studies support this simplified interpretation of the data. Indeed, there are many exceptions to this "rule."

A number of important electrophysiologic changes occur in atrial myocardium in response to an increase in vagus nerve activity. Acetylcholine, acting via its effect on muscarinic receptors, reduces the slope of spontaneous depolarization of the sinoatrial node pacemaker cells and results in a slowing of the heart rate. Acetylcholine also shortens the atrial refractory period and increases the heterogeneity of atrial refractoriness, effects that predispose to reentry (12,13). It appears that the relative sympathovagal balance is as important, or more important, than the absolute sympathetic or parasympathetic tone. Indeed, experimental regional cardiac denervation (e.g., withdrawal of sympathetic tone from a specific atrial site) can result in a relative increase in vagal tone without a change in the absolute vagal tone. This can result in regional shortening of the atrial refractory period, heterogeneity of atrial repolarization, and predisposition to induction of AF (14–16). This important interplay between sympathetic and parasympathetic tone is further underscored by the observation that AF induction in

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dogs occurs much more readily with infusion of isoproterenol and acetylcholine than with either isoproterenol or acetylcholine alone (17).

That increased vagal tone can predispose to the development of AF has been recognized since the initial description by Coumel et al. (18). Perhaps most exciting are the new therapeutic avenues that have been opened by our increased understanding of the autonomic influences that predispose to AF. Parasympathetic ganglia have been localized to discrete epicardial fat pads. Radiofrequency ablation of specific fat pads causes regional alterations of cardiac parasympathetic tone and, as a result, affects atrial refractory periods, atrioventricular nodal conduction properties, and heterogeneity of atrial conduction (15,19,20). In dogs, catheter ablation of parasympathetic nervous input to the atrium can abolish vagally mediated AF (21).

Loewi's (1) initial description of "vagusstuff" opened the door to important advances in our understanding of cardiac autonomic regulation. Similarly, improved understanding of the autonomic influences that predispose to AF will be critical to the development of novel therapies. While there is much that remains to be learned, specific pharmacologic, catheter, or device-based therapies that alter or regulate autonomic tone may someday prove to be useful weapons in the battle against AF.

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